REMARKS

Claims 1-3, 6, 7 and 9 are pending in the present application.

1. Claim amendments

Amendments to claim 1 are supported in the specification as filed, e.g., at page 10.

2. Anticipation Rejection over Baselga

Claims 1-3, 6, 7 and 9 are rejected as allegedly anticipated by Baselga et al., *J. Clin. Oncology* 14(3):737-744, March 1996. Applicants respectfully traverse this rejection.

The Office Action cites Baselga as disclosing "means for determining and measuring HER-2/neu ECD levels" in a serum sample from an individual with metastatic breast cancer that overexpresses HER2, where such measurements were "determined after treatment" with a recombinant humanized anti-Her2 monoclonal antibody (rhuMab).

MPEP §2131 states that "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." (Underlining added.) The present claim first recites "a method of screening a human subject in need of treatment for a solid epithelial tumor that overexpresses ErbB2 , as an aid in selecting between therapy with Trastuzumab alone and Trastuzumab combined with GW572016", where a first step comprises determining whether the tumor expresses $p95^{ErbB2}$. A second step correlates $p95^{ErbB2}$ expression with treatment choice: "where expression of $p95^{ErbB2}$ indicates said subject is more likely to exhibit a favorable clinical response to treatment that includes GW572016 in combination with trastuzumab, than to treatment with trastuzumab alone.

Baselga does not describe, either expressly or inherently, that presence of ECD indicates disease that is more suitable for treatment with combined trastuzumab and GW572016, compared to treatment with trastuzumab alone. Baselga does note that the serum level of rhuMAb was decreased in patients with circulating ECD of >500ng/ml (page 739, col. 2) and states that "no anticancer responses were observed in the group of patients with serum concentrations of $ECD^{HER2} \geq 500$ ng/mL" (page 742, col. 1). However, Baselga et al. do not provide any discussion of how levels of ECD correlate with treatment choice, or how levels of serum ECD correlate with the action of GW572016.

The Examiner states that Baselga discloses the "active step" of claim 1. The Examiner does not explain what is viewed as the "active step". Claim 1 recites determining whether the tumor expresses $p95^{ErbB2}$, and correlating this measurement with potential response to therapy, where expression of $p95^{ErbB2}$ indicates the subject is more likely to exhibit a favorable clinical response to treatment that includes GW572016 in combination with trastuzumab, than to treatment with trastuzumab alone. This correlation is not taught by Baselga et al.

Applicants request withdrawal of the present anticipation rejection over Baselga et al., as this reference does not expressly or inherently provide each and every element as set forth in the claim.

3. Anticipation rejection over US Patent Application Publication No. 2003/0219842.

Claims 1-3, 6 and 7 are rejected as allegedly anticipated by US Patent Application Publication No. 2003/0219842 A1. Applicants traverse this rejection.

The Office Action cites this publication as disclosing "means for determining and measuring HER-2/neu ECD levels in an individual's serum sample having solid tumors of the breast (mammary), ovary, colon, head and neck, bladder, liver and lung before, during and after anti-neoplastic treatment".

MPEP §2131 states that "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Underlining added.

US Patent Application Publication No. 2003/0219842 does not describe, either expressly or inherently, that presence of Her-2/neu ECD indicates disease that is more suitable for treatment with combined trastuzumab and GW572016, compared to treatment with trastuzumab alone. This publication relates HER-2/neu ECD levels to time to progression and overall survival time when elevated serum HER-2/neu levels and decreased EGFR ECD levels were found (see page 3, section 0020).

The Examiner states that this disclosure reads on the "active step" of claim 1. The Examiner does not explain what is viewed as the "active step". Claim 1 recites determining whether the tumor expresses $p95^{ErbB2}$, and correlating this measurement with potential response to therapy, where expression of $p95^{ErbB2}$ indicates the subject is more likely to exhibit a favorable

clinical response to treatment that includes GW572016 in combination with trastuzumab, than to treatment with trastuzumab alone. The cited reference does not teach or suggest any such correlation.

Applicants request withdrawal of the present anticipation rejection over US Patent Application Publication No. 2003/0219842, as this reference does not expressly or inherently provide each and every element as set forth in the claim.

4. Anticipation rejection over Harris et al.

Claims 1-3, 6 and 7 are rejected as allegedly anticipated by Harris et al., *J. Clin. Oncology* 19(6):1698-1706, March 2001. Applicants traverse this rejection.

The Office Action cites Harris as disclosing "assessment of HER-2 ECD in serum samples from breast cancer patients using an enzyme-linked immunoassay".

MPEP §2131 states that "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Underlining added.

Harris et al. do not describe, either expressly or inherently, that presence of Her-2/neu ECD indicates disease that is more suitable for treatment with combined trastuzumab and GW572016, compared to treatment with trastuzumab alone. Harris et al. used serum HER-2/neu EDC measurements as an indicator of HER2 overexpression, and state that they "studied the role of HER-2 as a predictor for response to high-dose chemotherapy and autologous bone marrow support" in patients with metastatic breast cancer. The therapies discussed did not include monoclonal antibodies directed to HER-2/neu (such as trastuzumab) or dual kinase inhibitors (such as GW572016). Harris et al. state that:

> Studies regarding the role of HER-2 ECD and outcome after chemotherapy are inconsistent. This may reflect differences in patient populations, the specific assay used, or differences in assessment of positivity. Perhaps as important, and frequently overlooked, is the specific regimen used and doses involved because mechanisms of resistance vary from one chemotherapeutic agent to another. With respect to HER-2 overexpression in the primary tumor, data suggest that these cells are inherently resistant to alkylator-based chemotherapy but may have an improved outcome with doxorubicin. (citations omitted) Whether increasing doses of alkylator-based therapy can overcome the drug resistance observed in HER-2-positive patients is unknown and the impetus for this study. Page 1702, col. 2, underlining added.

Harris et al. do not provide any discussion of how levels of serum ECD correlate with the action of GW572016.

The Examiner states that the disclosure of Harris et al. reads on the "active step" of claim 1 "and hence reads on" the method of claim 1. The Examiner does not explain what is viewed as the "active step". Claim 1 recites determining whether the tumor expresses $p95^{ErbB2}$, and correlating this measurement with potential response to therapy, where expression of $p95^{ErbB2}$ indicates the subject is more likely to exhibit a favorable clinical response to treatment that includes GW572016 in combination with trastuzumab, than to treatment with trastuzumab alone. Harris et al. do not teach or suggest this correlation.

Applicants request withdrawal of the present anticipation rejection over Harris et al., as this reference does not expressly or inherently provide each and every element as set forth in the claim.

5. Anticipation rejection over Molina et al.

Claims 1-3, 6, 7 and 9 stand rejected as allegedly anticipated by Molina et al., *Clinical Cancer Research* 8:347, February 2002. Applicants traverse this rejection.

The Office Action cites Molina as disclosing "a method of p95 analysis in breast cancer tissues implementing western blot analysis."

MPEP §2131 states that "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Underlining added.

Molina et al. do not describe, either expressly or inherently, that presence of Her-2/neu ECD indicates disease that is more suitable for treatment with combined trastuzumab and GW572016, compared to treatment with trastuzumab alone. Molina et al. did not correlate serum HER-2/neu ECD measurements with treatment selection.

The Examiner states that the disclosure of Molina et al. reads on the "active step" of claim 1 "and hence reads on" the method of claim 1. The Examiner does not explain what is viewed as the "active step". Claim 1 recites determining whether the tumor expresses $p95^{ErbB2}$, and correlating this measurement with potential response to therapy, where expression of $p95^{ErbB2}$ indicates the subject is more likely to exhibit a favorable clinical response to treatment

that includes GW572016 in combination with trastuzumab, than to treatment with trastuzumab alone.

Applicants request withdrawal of the present anticipation rejection over Molina et al., as this reference does not expressly or inherently provide each and every element as set forth in the claim.

6. Obviousness rejection over US Patent Application Publication 2003/0219842 in view of Baselga et al.

Claims 1-3, 6, 7 and 9 stand rejected under 35 USC §103(a) as obvious over US Patent Application Publication No. US 2003/0219842 , and further in view of Baselga et al. Applicants respectfully submit that the Examiner has not established a prima facie obviousness rejection.

A claimed invention is obvious only when the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art.

The present independent claim recites screening a human subject in need of treatment for a solid epithelial tumor that overexpresses ErbB2 , as an aid in selecting between therapy with Trastuzumab alone and Trastuzumab combined with GW572016, where combined treatment is indicated when the tumor is determined to expresses Her-2/neu p95. Neither of the cited references disclose the use of GW572016 in combination with trastuzumab; neither reference teaches or suggests that the expression of $p95^{ErbB2}$ indicates a subject is more likely to respond to treatment with combined trastuzumab and GW572016 than to treatment with trastuzumab alone.

The present inventors determined that the truncated form of Her-2/neu ($p95^{ErbB2}$) acts in a fundamentally different manner than intact ($p185^{ErbB2}$) Her-2/neu. They determined that $p95^{ErbB2}$ preferentially associates with ErbB3, in contrast to $p185^{ErbB2}$ which associates (heterodimerizes) with either EGFR or ErbB3. As stated in section 0004 of the published patent application (US 20060204966), a number of soluble ligands had been identified for EGFR, ErbB3, and ErbB4, but none had been identified for ErbB2, which was reported as being activated (phosphorylated) following heterodimerization.

The present inventors established that heregulin (a known ErbB3 ligand) stimulated $p95^{ErbB2}$ phosphorylation. They further found that GW572016 inhibited phosphorylation of $p95^{ErbB2}$ both in the presence and absence of heregulin (see e.g., section 0097 of published

application), whereas trastuzumab had limited effects on $p95^{ErbB2}$ phosphorylation in breast cancer xenografts (see Example 4).

Despite the differences in the biology of $p185^{ErbB2}$ and $p95^{ErbB2}$, the present inventors determined that GW572016 affects the activation of both intact and truncated Her-2/neu, whereas trastuzumab did not have the same effect. Tumors having the truncated form of Her-2/neu are thus more suitable for treatment with combined trastuzumab and GW572016 versus trastuzumab alone.

As stated in MPEP 2141, the framework for the objective analysis for determining obviousness under 35 USC 103 is stated in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are: (a) ascertaining the differences between the claimed invention and the prior art; and (b) ascertaining the differences between the claimed invention and the prior art; and (c) resolving the level of ordinary skill in the pertinent art.

As discussed herein, the claimed invention differs from the cited art in that the art does not teach or suggest that the expression of $p95^{ErbB2}$ by a solid epithelial tumor correlates with a biological situation amenable to treatment by combined trastuzumab and GW572016.

MPEP 2141 states that the key to supporting any rejection under 35 USC 103 is the clear articulation of the reasons why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting an obviousness rejection should be made explicit. The Court quoted *In re Kahn,* stating that "'[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" (*In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), cited with approval in KSR). The present obviousness rejection states only that:

> [I]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to assess the level of the ECD in a subject's serum after the treatment with trastuzumab as taught in the publication and Baselga. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in both references to determine the level of ECD in the sera of patients before and after cancer treatment in order to determine the course of disease and monitor disease progression and regression because it is art known [that] ECD serves as an indicator of treatment effectiveness.

However, the difference between the cited references and the subject matter of claim 1 is not addressed, namely the use of ECD as an aid in selecting appropriate treatment between trastuzumab alone and trastuzumab plus GW572016. Neither of the cited articles address this issue, or teach or motivate one skilled in the art to use, rather than trastuzumab alone, a combination of trastuzumab plus GW572016 when a solid epithelial tumor expresses $p95^{ErbB2}$.

Applicants submit that the *Graham* factual findings have not been established, and thus a *prima facie* case of obviousness has not been made.

Conclusion

In view of the above, withdrawal of the present rejections is requested.

Respectfully submitted,

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